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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,727	06/25/2003	Craig A. Rosen	PF596P1N	1552

22195 7590 07/19/2007

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/602,727	ROSEN ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2006 and 16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-37,41-46,51,52,55-67,69,70,79-86 and 97-104* is/are pending in the application.

4a) Of the above claim(s) *22-32,57-66,79-86 and 97-104* is/are withdrawn from consideration.

5)☒ Claim(s) *35-37, 41-46, 51-52, 55, 67* is/are allowed.

6)☒ Claim(s) *1, 5-21, 33, 34 and 69-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6-25-03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response and amendment filed 1-16-07 has been entered into the record. Claims 1, 5-37, 41-46, 51, 52, 55-67, 69, 70, 79-86, 97-104 are pending. Claims 2-438-40, 47-50, 53-54, 68, 71-78 and 87-96.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Specification

The disclosure is objected to because of the following informalities:

The peptide sequence "RKKR" at page 177 [0347] lacks an appropriate sequence identifier. Correction is required. Appropriate correction to the sequence listing or specification is required.

The use of trademarks at pages 147, 150 and 153 have been noted in this application. It should be capitalized wherever it appears *and be accompanied by the generic terminology.*

Information Disclosure Statement

The information disclosure statement filed 7-11-06 has been considered. An initialed copy is enclosed.

Election/Restrictions

Applicant's election with traverse of Group 1 in the response filed 7-7-06 is acknowledged. The traversal is on the ground(s) that the Specie B are not mutually

exclusive in that inhibition of receptor binding necessarily prevents or reduces the down stream affect of the receptor. This is not found persuasive because, there are as Applicants admit multiple receptors for anthrax toxin (PA). Applicants have not demonstrated that an antibody that blocks binding to one also blocks binding to the others and as such blocking one does not prevent translocation of EF or LF across a cell membrane mediated by other receptors. Applicant response relies on the concept that the species "may" have the same function. The reliance on "may" in the arguments is a clear indication that the downstream or alternative function *is not necessarily required* by the antibody. Therefore, the antibody "may not" have that specific function and as such would constitute a mutually exclusive specie of antibody that falls within the scope of the genus claim. Further, Applicants have not demonstrated that a single antibody binding to PA provides for all the recited functions set forth in specie B of the specie election and has not pointed to a particularly disclosed or claimed species that has all of the functions of the individual species set forth in Specie B, Group I. Applicants have not described the epitope to which an antibody binds that provides for all these functions and as such the specie election is maintained. The search and examination of all the different species would present an undue burden on the examiner, because each function requires a separate structure and functional evaluation.

The traversal of Specie A of heavy and light chain is moot in view of the amendment to the claims, since the species of the genus claim now share a common core structure and function. Applicants argue generic linking claims. The presence of the genus claim as recited in the amended claim is noted.

Applicants argue that search and examination of the method claims would not present an undue burden because the antibodies would reveal similar art. This is not persuasive, antibodies are alternatively used for diagnostics and therefore the search of the antibodies does not provide therapeutic search and examination. The restriction between the products and methods are maintained.

Applicants request for rejoinder is noted, when all claims are in condition for allowance the methods will be rejoined for examination.

The requirement is still deemed proper and is therefore made FINAL.

Claims 22-32, 57-66, 79-86, 97-104 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response of 7-7-06

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-21, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated antibody or fragment thereof that binds protective antigen 83 (PA83) of *Bacillus anthracis* comprising the heavy chain complementary determining regions: CDR1, CDR2, CDR3 as set forth in Table 1 (SEQ ID NO:53) and the light chain complementary determining regions: CDR 1, CDR2 and CDR3 as set forth in Table 1 (SEQ ID NO:53), wherein said antibody inhibits the binding of PA 83 to the anthrax receptor (ATR) or capillary morphogenesis protein 2, protease cleavage of PA into PA 20 and PA63 and pore formation and antibodies having a Kd less than or equal to 10^{-10} M, it does not reasonably provide enablement for changes to the CDR's or random combinations of CDR's from heavy and light chain variable regions and does not provide

enablement for antibodies that inhibit hepamerization of PA63 and PA63 binding to EF or LF, inhibition of PA-mediated translocation of EF or LF across a membrane or antibodies with Kd less than or equal to 10^{-11} M or 10^{-12} M. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficiently enabling description of the claimed invention. The breadth of the instant claims encompass a specific binding member in which fewer than all of the three complementary determining regions (CDRs) found in the heavy chain variable region and/or fewer than all of the three CDRs found in the light chain variable region are defined, random combinations of different heavy and light chains and also does not particularly define the antigen that the antibody binds. Applicant has disclosed human sFv PA 83 binding antibodies, and the corresponding amino acids encoding the variable heavy and light chain regions and the corresponding CDR's which have the functions as set forth surpa. In each case the specific binding member has the same three CDRs of the heavy chain variable region and the same three CDRs of the light chain variable region. The specification as filed provides no working examples showing that fewer than all six CDRs of the antibody are required for binding to PA83. Therefore, the description of different CDR3's from different sFv's in Table 4 of the specification is insufficient to provide a description of the now claimed genus of 85% identical antibodies that bind PA 83. Neither does the specification appear to provide sufficient guidance as to which subsets of CDRs could be used in a specific binding member comprising less than all six CDRs and still maintain PA83 binding and which specific residues could be mutated in combination with the other CDR's. Without sufficient guidance, it would require undue experimentation of the skilled artisan to make specific binding members which could bind PA but which comprised fewer than all six CDRs from parental monoclonal antibody. The state of the art recognized that in general all three CDRs of the heavy chain variable region AND all three CDRs of the light chain variable region were important for

determining the ability of an antibody in any of a variety of forms (scFv, whole, etc.) to bind antigen. For example, Bendig (Methods: A Companion to Methods in Enzymology 1995; 8:83-93) reviews that the general strategy for "humanizing" antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire document, but especially Figures 1-3). Similarly, the skilled artisan recognized a "chimeric" antibody to be an antibody in which both the heavy chain variable region (which comprises the three heavy chain CDRs) and the light chain variable region (which comprises the three light chain CDRs) of a rodent antibody or the human CDRs with other human framework regions are recombined with constant region sequences from a human antibody of a desired isotype (see entire document, but especially Figures 1-3). The state of the art recognized that it would be highly unpredictable that a specific binding member comprising an antibody variable region but comprising less than all six CDRs of a parental antibody with a desired specificity would bind the same antigen as the parental antibody. Thus the minimal structure which the skilled artisan would consider predictive of the function of binding PA83 includes six CDRs (three in the heavy chain variable region and three in the light chain variable region) from the same parental antibody in the context of an antibody framework. In addition, the skilled artisan recognized that single CDRs with the same amino acid sequence could be found in antibodies with diverse specificities. In particular, antibodies which have not yet undergone affinity maturation may still utilize germline heavy and light chain sequences. Between antibodies utilizing the same germline heavy or light chain gene the skilled artisan would expect to find that one or more of the heavy and/or light chain CDRs were the same as that of an antibody with a different specificity, particularly CDRs 1and 2 which are germline encoded completely in the variable region. The same CDR may also occur in antibodies having somatic mutations that bind different antigens. Thus it would be highly unpredictable that the instantly recited specific binding member comprised of fewer than all six CDRs (three CDRs defined in the heavy chain

variable region and three CDRs defined in the light chain variable region) of a particular reference antibody would have the same specificity as the reference antibody. Further, the antibody structure is not a random combination of heavy and light chain variable regions. The antibody paratope, binds an epitope on an antigen. The paratope of the antibody is highly specific and provides for a specific three-dimensional pocket in which the epitope of the antigen binds. The pocket is dependent on the specific primary structure of the complementary determining regions provided in a framework of other regions in a specific order. The specification does not describe nor enable the random combination of heavy and light chain variable regions or CDR's fragments therefrom to prepare a fully human monoclonal antibody. The cloned antibodies presented in the specification are apparently from different gremlins and as such one of skill in the art can simply not predict what effect random shuffling of heavy and light chain variable regions or CDR's therefrom will have on antibody binding per se and specificity of the antibody with respect to antigen. The specification lacks a single working example of combining different parental derived CDRs and different parental derived heavy and light chain variable regions on binding to PA or binding to anthrax serotoxin in general. Furthermore, the specification lacks written description of any antibody that meets the limitations of binding affinity in claims 15 and 16. The specification lacks guidance as to how to achieve the very high affinity antibodies claimed. As such, one skilled in the art would not recognize which sequences or described antibodies meet this claimed limitation. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. A reasonable correlation must exist between the scope of the claims and scope of

enablement set forth. Given the recognized unpredictable nature of making specific binding members with a desired specificity having fewer than all six CDRs from a reference antibody and the lack of sufficient guidance provided in the specification; the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

Claims 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's referral to the deposit of the claimed cell line PTA-4796 on page 17 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR §1.801-1.809 have been met.

Since the specification indicates that the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number *stating that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application* is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Status of the Claims

Claims 1, 5-21, 33, 34 and 69-70 stand rejected. Claims ~~35-52~~ 35-37, 41-52, 55, 67 stand allowed.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Examiner Jeffrey Siew can be reached on 571-272-0787.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy, Ph.D.
Primary Examiner
Art Unit 1645